Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control

Daan Nevens [a,*], Fréderic Duprez [b], Jean Francois Daisne [c], Ruveyda Dok [d], Ann Belmans [e], Mia Voordeckers [f], Danielle Van den Weyngaert [g], Wilfried De Neve [b], Sandra Nuyts [a]

[a] Department of Radiation Oncology, KU Leuven – University of Leuven, University Hospitals Leuven; [b] Department of Radiotherapy, Ghent University Hospital; [c] Department of Radiation Oncology, Clinique et Maternité Sainte-Elisabeth, Namur; [d] Laboratory of Experimental Radiotherapy, Department of Oncology, Katholieke Universiteit Leuven (KU Leuven); [e] Leuven Biostatistics and Statistical Bioinformatics Centre, University of Leuven; [f] Department of Radiation Oncology, UZ Brussel, Vrije Universiteit Brussel; and [g] Department of Radiation Oncology, ZNA Middelheim, Antwerp, Belgium

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 3 August 2016
Accepted 4 August 2016
Available online xxxx

Keywords:
Head and neck cancer
Radiotherapy
Elective nodes
Dose reduction

ABSTRACT

Background and purpose: A multi-center prospective randomized clinical trial has been performed investigating whether a reduction of the dose to the elective nodal sites in head and neck cancer delivered by intensity modulated radiotherapy (IMRT) would result in a reduction of late side effects without compromising tumor control.

Materials and methods: Two hundred patients were included. The prescription dose to the elective nodal volumes was a normalized iso-effective dose in 2 Gy fractions (NID_{2Gy}) of 50 Gy in the standard arm and of 40 Gy in the experimental arm. Late toxicity was scored at 6, 12, 18 and 24 months using the RTOG scoring system.

Results: We observed a trend toward less dysphagia at 6 months in the experimental arm, however this was not confirmed after longitudinal analysis. Regarding moderate salivary gland toxicity we observed lower incidence of salivary gland toxicity $\geqslant$grade 1, at 6 ($p = 0.01$) and 18 months ($p = 0.03$).

Results: After two years of follow up, we did not observe significant differences in estimated local failure rate (14.1% in the 40 Gy arm vs 14.4% in the 50 Gy arm), estimated regional failure rate (13.0% vs 5.5% in the 40 and the 50 Gy arm respectively), estimated metastatic recurrence (13.4% vs 18.5% in the 40 and the 50 Gy arm respectively), estimated disease-free survival (57.9% vs 65.3% in the 40 and the 50 Gy arm respectively) nor estimated overall survival (72.0% vs 73.2% in the 40 and the 50 Gy arm respectively).

Conclusions: In our study population there was no statistically significant difference regarding survival and estimated recurrence rates between both arms of this study. We found a trend toward less dysphagia at 6 months (however not significant after longitudinal analysis) and found a significant reduction of any salivary gland toxicity at 6 and 18 months in the 40 Gy arm.

Radiotherapy (RT) with curative intent for head and neck cancer (HNC) results in a significant amount of side effects due to unwanted doses in normal tissues surrounding the target volume [1,2]. One of the most important late side effects limiting quality of life is swallowing dysfunction (dysphagia).

Following the introduction of more aggressive treatment strategies for HNC in the last decades, more attention has been addressed to late dysphagia [3–5]. Both concurrent chemotherapy and accelerated fractionation have been identified as significant predictive factors to develop dysphagia [3–5,6]. The dose delivered to the pharyngeal constrictor muscles plays a crucial role in the development of severe late dysphagia [7–11]. Our research group demonstrated in a previous paper that a dose de-escalation to the elective lymph nodes in HNC results in significantly less dose to these functionally important structures and less severe dysphagia at 3 months following treatment [12].

In this paper we report the results of a multi-center prospective randomized clinical trial that investigated whether a reduction of the dose to the elective nodal sites would result in a reduction of late dysphagia without compromising regional control.

* Corresponding author at: Herestraat 49, 3000 Leuven, Belgium.
E-mail address: daan.nevens@uzleuven.be (D. Nevens).

http://dx.doi.org/10.1016/j.radonc.2016.08.009
0167-8140/

Material and methods

A prospective randomized multicenter non-inferiority phase III study was set up between 6 centers. Inclusion criteria were previously untreated, histologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx or cervical lymph node metastases of unknown primary cancer (CUP). Patient work-up was done according to institutional guidelines. T1–T2N0 were allowed, if prophylactic neck irradiation was performed. Patients were older than 18 years with a Karnofsky performance status $\geqslant$70%. The decision for primary (chemo-)RT with curative intent had to be made after a multidisciplinary meeting at each participating center. Concurrent chemotherapy was allowed, as well as pretreatment lymph node dissection. Local ethics committee approval was obtained before start of the study and all patients gave written informed consent. Patients were randomized to two treatment arms (experimental arm A and standard arm B). A total of 200 patients were included in the study (100 for each arm). To minimize the influence of center-specific parameters randomization was performed per center.

All macroscopically affected tumor sites were treated up to a normalized iso-effective dose in 2 Gy fractions (NID2Gy) of 70 Gy. Fractionation schedule and total dose delivered to the primary tumor and affected lymph nodes were left to the discretion of each individual center. An overview of the different fractionation schedules and CTV-PTV margins can be found in the preliminary analysis of this study [12]. For the elective nodal volumes, patients randomized in arm A (experimental arm) were treated up to a NID2Gy of 40 Gy. For arm B (control arm) the elective nodal volumes were treated up to a NID2Gy of 50 Gy (Fig. 1) [12].

All patients were treated with IMRT using either an in-house developed extension of the GRATIS-software by Sherouse coupled to dose calculation using Pinnacle version 6.2b or the commercially available treatment planning systems (Eclipse®, Palo Alto; Tomotherapy High-art®, Madison) and delivered using 6 or 10 MV photons using either a step-and-shoot, a sliding window or rotational technique. Patient set-up and position verification was performed according to each center's discretion.

Late toxicity was scored at 6, 12, 18 and 24 months using the RTOG scoring system.

Assessment of HPV status

Since HPV status was not considered in the first paper, this was currently assessed [12]. For all patients with oropharyngeal tumors, formalin-fixed, paraffin-embedded (FFPE) tissue was centralized (University Hospital of Leuven) for HPV-status determination. HPV testing was performed using a previously validated algorithm using p16 immunohistochemistry (IHC) followed by HPV-polymerase chain reaction (PCR) [13–15]. A tumor was regarded as HPV related when both p16 IHC as well as HPV-PCR were positive.

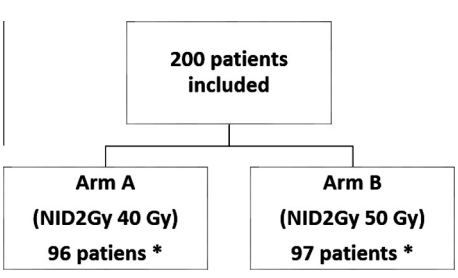

Fig. 1. Consort diagram of the study. *Information of 1 participating center (7 patients) could not be retrieved before close-out date of this analysis, yielding 193 patients for analysis.

For p16 IHC a purified mouse anti-human p16 antibody (G175-405, BD Pharmigen) was used. Sections were scored as p16 positive when clear p16 immunoreactivity was seen in at least 50% of cells [14]. DNA was extracted from PPFE sections using the QIAamp DNA FFPE Tissue kit. Concentration and purity where then defined with spectrophotometry. HPV status was determined with a PCR reaction using the GP5+/6+ primer set.

Endpoints of the study

The primary endpoint of the study was the rate of dysphagia at 6 months of follow-up.

Secondary endpoints of the study were: local, regional and distant control; recurrence and site of recurrence; overall, disease-free and disease-specific survival; stiffness of the neck; skin toxicity; salivary gland toxicity and mucosal integrity.

General considerations of the statistical analysis

Assuming a 70% rate of late dysphagia $\geqslant$grade 1 will be unacceptable and a 50% rate will be expected ($\alpha = 0.05$, $p = 0.8$, two-tailed test) the power calculation of the study resulted in 200 eligible patients (100 patients per arm).

All tests were 2-sided and assessed at a significance level of 5%. Due to the exploratory nature of the study, no adjustments were made to the significance level to account for multiple testing. All analyses have been performed using SAS System for Windows (version 9.4).

Statistical analysis of the late toxicity endpoints

The following toxicity endpoints were assessed: dysphagia, stiffness of the neck, skin toxicity, salivary gland toxicity and mucosal integrity.

A chi-square test for trend was performed at each time-point to assess whether there was a statistically significant difference between the two randomized groups. Because these tests are susceptible to bias due to missing data, early withdrawals and/or early mortality, a longitudinal analyses using Generalized Estimating Equations (GEE) was also performed since it has been documented that GEE models can provide unbiased estimates even in such circumstances if the condition of Missingness at Random (MAR) holds. The above toxicity endpoints were analyzed using a GEE proportional odds model with an independent correlation matrix to account for the clustering of the data.

Primarily, the longitudinal proportional odds model includes a factor for randomized treatment, visit and their interaction. The inclusion of the interaction allows for the treatment effect to vary between visits. The effect of randomized treatment was estimated from the GEE model at each visit.

In addition, analyses were done for the probability of having severe ($\geqslant$grade 3) and moderate ($\geqslant$grade 1) toxicity. Since these are binary endpoints, the longitudinal analyses were done by means of a GEE logistic regression model.

Statistical analysis of outcome

Overall and disease-free survival was estimated using Kaplan–Meier methodology. Differences between treatments were assessed by means of a log-rank test.

Competing risk methodology was used for local, regional or distant failure, whereby death was considered to be a competing risk, to take the fact into account that patients who died cannot have a recurrence in the future. Event rates were estimated using cumulative incidence functions (CIF) and comparisons were made using Gray's test.

Please cite this article in press as: Nevens D et al. Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.08.009

Location of recurrences

In case of a regional recurrence, the recurrence was contoured on the CT study and rigidly co-registrated with the initial pretreatment CT study. Co-registration was done automatically using Eclipse® Treatment Planning system. If this was not accurate, manual registration was performed. To determine the exact location of recurrence the method described by Dawson et al. was used [13]. The recurrences were classified as 1) "in-field," in which 95% or more of the recurrence volume (Vrecur) was within the 95% isodose; 2) "marginal," in which 20% to 95% of Vrecur was within the 95% isodose; or 3) "outside," in which less than 20% of Vrecur was within the 95% isodose.

Results

Patients

Between May 2008 and May 2011, 200 patients were included and randomized. Treatment characteristics of 7 patients could not be retrieved before close-out date of this analysis, yielding 193 patients for analysis (96 in the experimental arm and 97 in control arm). Patient characteristics are depicted in Table 1.

The study included 83 patients with an oropharyngeal tumor; 41 in the 40 Gy and 42 in the 50 Gy arm. 17 patients (20,5%) of these 83 patients had an HPV positive tumor; 60 patients (72,5%) had an HPV negative tumor and 6 patients (7%) had an unknown

Table 1
Patient and treatment characteristics. KI, Karnofsky index; OTT, overall treatment time; AJCC, American Joint Committee on Cancer.

		Study arm (n = 96)		Control arm (n = 97)		p-Value
			(%)		(%)	
Social status	Single	27	28	27	28	0.9
	Partner	52	54	57	59	
	Unknown	17	18	13	13	
Age	<70	80	83	85	88	0.4
	>70	16	17	12	12	
Gender	M	75	78	84	87	0.13
	F	21	22	13	13	
KI performance status	>80	70	73	67	69	0.75
	<80	26	27	28	29	
	Unknown	1	1	2	2	
Tumor site	CUP	4	4	5	5	1
	Larynx	18	19	18	19	
	Oral cavity	11	11	9	9	
	Hypopharynx	22	23	23	24	
	Oropharynx	41	43	42	43	
	HPV+	7		10		0.35
	HPV−	31		29		
	Unknown	3		3		
AJCC stage	I	1	1	0	0	1
	II	10	10	12	12	
	III	19	20	25	26	
	IV	66	69	60	62	
T-stage	*x*	4	4	5	5	0.1
	1	1	1	4	4	
	2	32	33	40	41	
	3	34	35	30	31	
	4	25	26	18	19	
N-stage	*x*	1	1	0	0	1
	0	22	23	26	27	
	1	16	17	14	14	
	2	54	56	56	58	
	3	3	3	1	1	
Pretreatment dysphagia	Grade 0	52	54	54	56	0.16
	Grade 1	26	27	32	33	
	Grade 2	17	18	10	10	
	Grade 3	1	1	1	1	
Neo-adjuvant chemotherapy	No	91	95	95	98	0.28
	Yes	5	5	2	2	
Pretreatment lymph node dissection	No	79	82	78	80	0.85
	Yes	17	18	19	20	
Prescribed dose (in Gy) for PTV_{ther}	Mean	70		70		0.37
	SD	1.6		1.9		
OTT (days)	Mean	45		45		0.2
	SD	2.3		2.6		
Planned dose reached	Yes	94	98	93	96	0.68
	No	2	2	4	4	
Concurrent systemic treatment	Platinum based	56	58	61	63	0.44
	Targeted therapy	5	5	7	7	
	Other	1	1	0	0	
	No	34	35	29	3	

Please cite this article in press as: Nevens D et al. Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.08.009

HPV status. The summary of the result of the HPV assessment can be found in Table 1.

Toxicity

Following a chi square test, we observed a trend toward less dysphagia at 6 months ($p = 0.02$) and at 24 months ($p = 0.07$) in the 40 Gy group. The difference in grade 2 dysphagia at 6 months stands out with 3.8% in the 40 Gy arm versus 20.8% in the 50 Gy arm. However, when accounting for early drop-outs and deaths using longitudinal analyses, no statistically significant differences regarding dysphagia between both treatment groups could be observed (Table 2). The interaction between visit and treatment was found to be not significant ($p = 0.80$) and when removing the interaction from the model, the odds ratio between 40 Gy and 50 Gy for observing a lower grade of dysphagia was in favor of the 40 Gy group, however clearly not significant; 1.40 (95% confidence interval 0.93 to 2.10, $p = 0.11$). Furthermore, regarding moderate dysphagia ($\geqslant$grade1) or severe dysphagia ($\geqslant$grade 3), we did not observe significant differences between both groups.

We observed a lower incidence of any salivary gland toxicity ($\geqslant$grade 1), at 6 and 18 months ($p = 0.01$ and $p = 0.04$, respectively) in the 40 Gy arm (Table 3). This was confirmed by the longitudinal analyses ($p = 0.01$ and 0.03, respectively). The interaction between treatment and visit was found to be not significant ($p = 0.14$) and when removing the interaction from the model, the odds ratio between the 40 Gy group versus the 50 Gy group for having no salivary gland toxicity was in favor of the 40 Gy arm; 1.88 (95% CI 1.07 to 3.31, $p = 0.03$).

No significant difference between both groups was detected regarding stiffness of the neck, salivary gland toxicity $\geqslant$grade 3, skin problems and mucosal integrity.

Outcome

Median follow-up was 34.2 months (range 2.2–79.0). We did not observe significant differences in outcome and survival between both groups at 6, 12, 18 and 24 months (Table 4).

After 2 years, estimated overall survival was similar in both groups (72% and 73% in the 40 Gy and 50 Gy group, respectively

Table 2
Prevalence of dysphagia at each time-point.

Dysphagia							
	Randomisation	G 0	G 1	G2	G3	Total	P(GEE)
Month 6	40 Gy	48 (61.5%)	27 (34.6%)	3 (3.8%)	0	78	0.06
	50 Gy	37 (51.4%)	20 (27.8%)	15 (20.8%)	0	72	
Month 12	40 Gy	45 (67.2%)	14 (20.9%)	7 (10.4%)	1 (1.5%)	67	0.21
	50 Gy	37 (56.9%)	18 (27.7%)	6 (9.2%)	4 (6.1%)	65	
Month 18	40 Gy	39 (68.4%)	12 (21.0%)	6 (10.5%)	0	57	0.16
	50 Gy	33 (55.0%)	19 (31.7%)	8 (13.3%)	0	60	
Month 24	40 Gy	39 (73.6%)	12 (22.6%)	2 (3.8%)	0	53	0.15
	50 Gy	34 (63.0%)	12 (22.2%)	6 (11.1%)	2 (3.7%)	54	

Using a GEE proportional odds model including treatment, visit and their interaction, the interaction was found not significant ($p = 0.8332$). When dropped from the model, the odds ratio between 40 Gy and 50 Gy for observing a lower grade toxicity was 1.40 (95% confidence interval 0.93 to 2.10, p-value = 0.1088).

Table 3
Prevalence of salivary gland toxicity $\geqslant$ grade 1 and salivary gland toxicity $\geqslant$ grade 3 at each time-point.

		$\geqslant$grade1 salivary gland toxicity	Total	P(GEE)	$\geqslant$grade3 salivary gland toxicity	Total	P(GEE)
Month 6	40 Gy	55 (68.7%)	80	0.01	2 (2.5%)	80	0.7
	50 Gy	63 (86.3%)	73		3 (4.1%)	73	
Month 12	40 Gy	47 (71.2%)	66	0.23	3 (4.5%)	66	1.0
	50 Gy	53 (80.3%)	66		2 (3.0%)	66	
Month 18	40 Gy	37 (63.8%)	58	0.03	2 (3.4%)	58	1.0
	50 Gy	49 (81.7%)	60		2 (3.3%)	60	
Month 24	40 Gy	34 (63.0%)	54	0.84	1 (1.8%)	54	1.0
	50 Gy	35 (64.2%)	54		0 (0.0%)	54	

Using a GEE logistic regression model including treatment, visit and their interaction, the interaction was found not significant ($p = 0.1442$). When dropped from the model, the odds ratio between 40 Gy and 50 Gy for having no salivary gland toxicity was 1.88 (95% confidence interval 1.07 to 3.31, p-value = 0.0281).

Table 4
Overview of the estimated outcome of the study and 95% confidence interval and corresponding p values.

	6 months		12 months		24 months		p value
	40 Gy arm	50 Gy arm	40 Gy arm	50 Gy arm	40 Gy arm	50 Gy arm	
OS	92.6% (85–96.4)	95.7% (88.9–98.4)	82.7% (73.3–89.0)	85.7% (76.6–91.4)	72.0% (61.4–80.2)	73.2% (62.3–81.4)	0.73
DFS	83.0% (73.7–89.2)	85.0% (76.0–90.8)	70.0% (59.6–78.2)	69.9% (59.5–78.1)	57.9% (47.1–67.2)	65.3% (54.6–74.1)	0.41
LFR	4.3% (1.4–9.8)	3.2% (0.9–8.4)	10.7% (5.5–18.0)	8.7% (4.0–15.5)	14.1% (7.9–22.1)	14.4% (8.1–22.5)	0.99
RFR	7.4% (3.3–13.9)	2.2% (0.4–7.0)	11.8% (6.2–19.3)	5.5% (2.0–11.6)	13.0% (7.1–20.8)	5.5% (2.0–11.6)	0.08
LRFR	10.6% (5.4–17.8)	5.4% (2.0–11.3)	20.3% (12.8–29.1)	10.8% (5.5–18.2)	23.7% (15.6–32.8)	15.4 (8.9–23.7)	0.14
MR	4.3% (1.4–9.8)	9.8% (4.8–16.9)	6.4% (2.6–12.6)	17.4% (10.4–25.8)	13.4% (7.3–21.3)	18.5% (11.3–27.1)	0.25

For OS and DF, differences were assessed using a log-rank test. For LFR, RFR, LRFR and MR, differences between groups were assessed using Gray's testing, considering death as a competing risk.
OS: overall survival; DFS: disease-free survival; LFR: local failure rate; RFR: regional failure rate; LRFR: loco-regional failure rate; MR: metastatic recurrence.

Please cite this article in press as: Nevens D et al. Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.08.009

($p = 0.73$)). Furthermore no statistically significant difference was found in the estimated disease free survival at 2 years ($p = 0.41$), although a lower rate was observed in the 40 Gy group (58%) in comparison with the rate in the 50 Gy group (65%).

We did not observe statistically significant differences in estimated locoregional recurrence rates between both groups at 6, 12 and 24 months. However, after 2 years of follow-up, the cumulative incidence of locoregional recurrence was higher (24%) in the 40 Gy arm when compared to the 50 Gy arm (15%) ($p = 0.14$). The estimated local recurrence rate was 14% in both groups.

Regarding regional recurrences, we see a difference in estimated risk between both groups, however not significant (p = 0.08): 13% vs. 6% in the 40 Gy arm and 50 Gy arm at 2 years, respectively (fig. 2). In total, 17 regional recurrences have been observed during follow-up (Table 5). Three of seventeen (18%) occurred in the PTV elective (2 in the 40 Gy arm and 1 in the 50 Gy arm) whereas 12 regional recurrences were located in the high dose volume (11 in the GTV, 1 in the PTV). Two regional recurrences occurred outside the planning volume in the 40 Gy arm.

Of the 17 patients with regional recurrence, 6 underwent salvage neck dissection. Palliative chemotherapy was started in 4 patients, as salvage neck dissection was not considered to be advantageous because of synchronous metastases ($n = 3$) or an irresectable relapse ($n = 1$). No further therapy was provided in 7 patients because these patients opted not to be treated.

Regarding estimated metastatic risk, we observed no significant differences; however we observed a lower incidence (13.4%) in the 40 Gy arm when compared to the 50 Gy arm (18.5%) after 2 years of follow up ($p = 0.25$) (fig. 3).

Table 5
Site of the regional recurrences.

Recurrence	40 Gy ARM	50 Gy ARM
GTV lymph node	6	5
PTV lymph node	1	0
Outside planning volume	2	0
PTV elective	2	1

PTV: Planning Target Volume.
GTV: Gross Tumor Volume.

Discussion

In this paper we describe the late toxicity and outcome of a multicenter randomized controlled trial reducing the dose to the elective lymph nodes in patients treated for head and neck cancer.

The primary endpoint of this study was late dysphagia as this is the most important quality of life compromising toxicity after curative treatment of HNC [2]. Altered fractionation schedules, concomitant chemotherapy and oropharyngeal tumor location are associated with more dysphagia [6]. With the incidence of oropharyngeal carcinoma in the western world on the rise, the widespread use of concomitant chemoRT and the use of altered fractionation schedules, prevention of late dysphagia will be of upmost importance in optimizing the quality of life in these patients [16–19].

Our preliminary analysis demonstrated that a dose de-escalation to the elective lymph nodes, significantly reduced the volume of the swallowing apparatus irradiated up to a high dose without compromising target coverage and dose homogeneity. Clinically this dose reduction resulted in significantly less grade $\geqslant 3$ dysphagia in the de-escalated arm 3 months after treatment with similar LRC and DFS rates [12]. We also observed a better quality of life in the 40 Gy arm (unpublished data, recently submitted to Radiotherapy and Oncology).

The current updated results show a trend toward less late dysphagia, however not confirmed after longitudinal analysis. Furthermore, we observed significantly less moderate salivary gland toxicity in the 40 Gy arm at 6 and 18 months, confirmed after longitudinal analysis. This is a somewhat unexpected finding, since

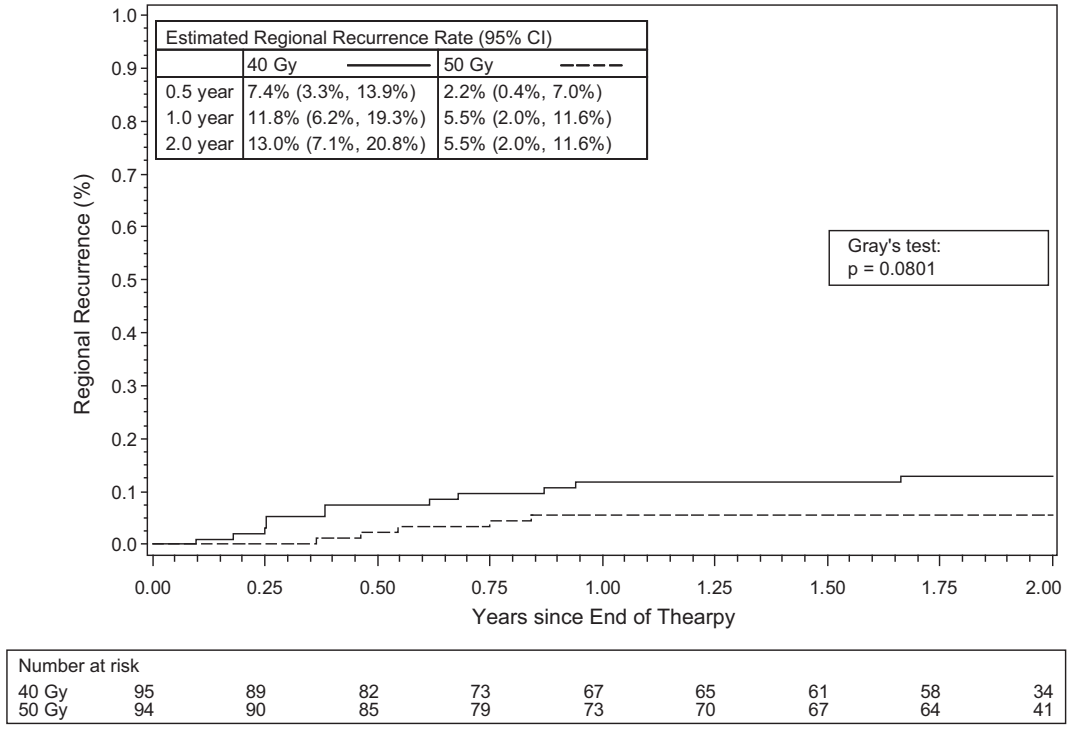

Fig. 2. Cumulative incidence curves for regional recurrence.

Please cite this article in press as: Nevens D et al. Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.08.009

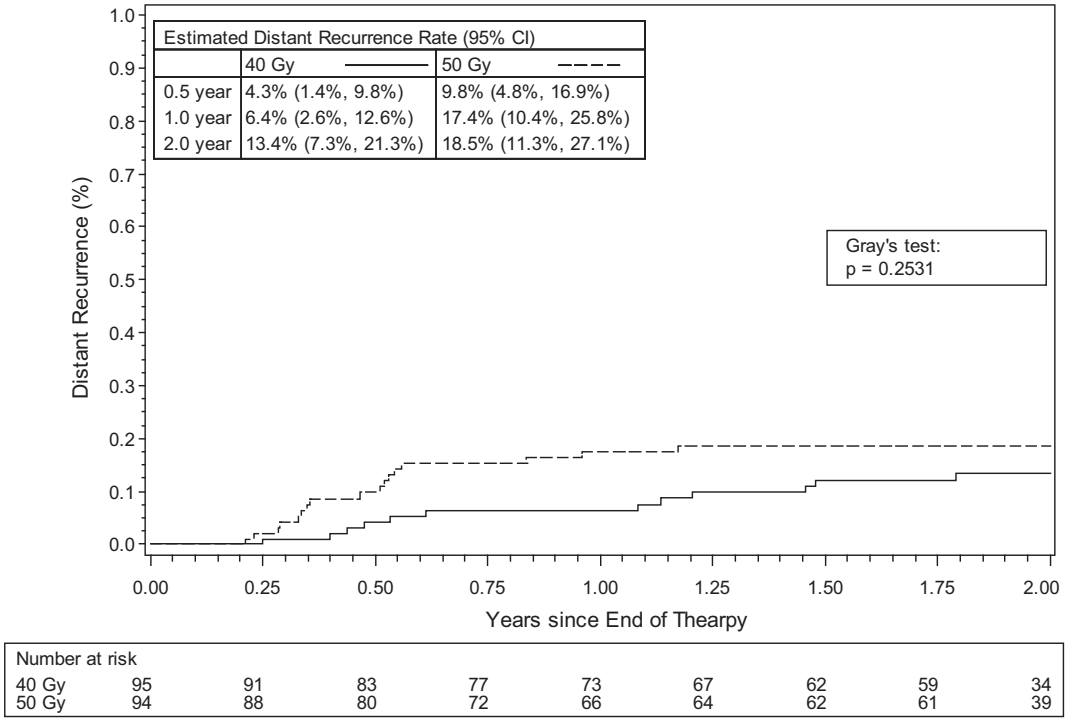

Fig. 3. Cumulative incidence curves for metastatic risk.

there was no significant difference between doses tot the parotid glands in both treatment arms, as published in our first paper.

No significant difference between both groups was detected regarding stiffness of the neck, severe salivary gland toxicity, skin problems and mucosal integrity. A possible explanation for this is the fact that the high doses given to the PTV of the primary tumor were identical in both groups.

Outcome in terms of local, regional and distant control and survival did not differ significantly between the groups after two years of follow up. In the 40 Gy arm however, we observed a higher absolute number of all regional recurrences (i.e. in the elective neck as well as in pre-existing pathological lymph nodes). It was reassuring that there were only 2 regional recurrences in the elective neck outside the high-dose PTV in the 40 Gy arm and 1 in the 50 Gy arm. Obviously, these numbers are too small to conclude that more elective neck recurrences would occur when lowering the dose in the elective neck from 50 to 40 Gy NID_{2Gy}.

It could be hypothesized that lowering the dose for subclinical disease could result in less control and thereby in higher numbers of distant metastases [20]. We did not observe more distant metastases in the de-escalated group; on the contrary, a higher absolute number of patients had distant metastases in the 50 Gy group (not significant). This finding is reassuring with respect to the possibility to enhance occurrence of distant metastases when lowering the dose to the elective neck.

So far, no randomized data on dose de-escalation to the elective nodal volume in head and neck cancer were published. Therefore the choice of 40 Gy for our de-escalation arm was quite arbitrarily chosen, although supported by two non-randomized analyses [21,22].

We hereby present the first study that demonstrates the non-inferiority of dose de-escalation in the elective neck to 40 Gy in terms of regional control in the elective neck. Meanwhile, a follow-up multicenter trial has been conducted comparing dose de-escalation in the elective neck using adaptive RT in reduced volumes of the elective neck in an attempt to further diminish treatment-induced toxicity. Combining data of both studies can give us more information on the safety of dose-reduction to the elective nodal volume.

Although the main purpose of the trial was to study the effect of a dose-reduction to 40 Gy-equivalent dose in the elective neck, a large heterogeneity remains between the treating centers in terms of fractionation schedules, dose prescription to the high-dose PTV, expansion margins from CTV to PTV, patient positioning protocols and the use of concurrent chemotherapy. In order to avoid confounding effects of this center-dependent heterogeneity, the trial randomization was performed per center.

Conclusions

Dose de-escalation to the elective nodal volume in HNC from a 50 to a 40 Gy-equivalent dose results in a trend toward less dysphagia at 6 months and less moderate salivary gland toxicity without significant differences in disease control or survival.

Conflict of interest

None of the authors has a conflict of interest in connection with the paper and the material is not under publication or consideration for publication elsewhere.

Acknowledgments

The project was funded by Kom Op Tegen Kanker. Study organization and data collection were performed by Rita Aerts.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.08.009.

References

[1] Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26:3582–9.
[2] Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, et al. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 2008;26:3770–6.
[3] Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843–54.
[4] Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011;100:33–40.
[5] Nuyts S, Dirix P, Clement PM, et al. Impact of adding concomitant chemotherapy to hyperfractionated accelerated radiotherapy for advanced head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2009;73:1088–95.
[6] Langendijk JA, Doornaert P, Rietveld DH, et al. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. Radiother Oncol 2009;90:189–95.
[7] Dirix P, Abbeel S, Vanstraelen B, et al. Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: dose–effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2009;75:385–92.
[8] Levendag PC, Teguh DN, Voet P, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose–effect relationship. Radiother Oncol 2007;85:64–73.
[9] Christianen ME, Schilstra C, Beetz I, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. Radiother Oncol 2012;105:107–14.
[10] Duprez F, Madani I, De Potter B, Boterberg T, De Neve W. Systematic review of dose-volume correlates for structures related to late swallowing disturbances after radiotherapy for head-and-neck cancer. Dysphagia 2013;28:337–49.
[11] Eisbruch A, Kim HM, Feng FY, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys 2011;81:e93–9.
[12] Nuyts S, Lambrecht M, Duprez F, et al. Reduction of the dose to the elective neck in head and neck squamous cell carcinoma, a randomized clinical trial using intensity modulated radiotherapy (IMRT). Dosimetrical analysis and effect on acute toxicity. Radiother Oncol 2013;109:323–9.
[13] Dok R, Kalev P, Van Limbergen EJ, Asbagh LA, Vázquez I, Hauben E, et al. P16INK4a impairs homologous recombination-mediated DNA repair in human papillomavirus-positive head and neck tumors. Cancer Res 2014;15:1739–51.
[14] Van Limbergen EJ, Dok R, Laenen A, Hauben E, Van den Weyngaert D, Voordeckers M, et al. HPV-related oropharyngeal cancers in Flanders (Belgium): a multicenter study. B-ENT 2014;10:7–14.
[15] Dawson LA, Anzai Y, Marsh L, et al. Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2000;46:1117–26.
[16] Nasman A, Attner P, Hammarstedt L, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? Int J Cancer 2009;125:362–6.
[17] Auluck A, Hislop G, Bajdik C, et al. Trends in oropharyngeal and oral cavity cancer incidence of human papillomavirus (HPV)-related and HPV-unrelated sites in a multicultural population: the British Columbia experience. Cancer 2010;116:2635–44.
[18] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.
[19] Nevens D, Nuyts S. HPV-positive head and neck tumours, a distinct clinical entity. B-ENT 2015;11:81–7.
[20] Withers HR, Peters LJ, Taylor JM. Dose–response relationship for radiation therapy of subclinical disease. Int J Radiat Oncol Biol Phys 1995;31:353–9.
[21] Bedi M, Firat S, Semenenko VA, et al. Elective lymph node irradiation with intensity-modulated radiotherapy: is conventional dose fractionation necessary? Int J Radiat Oncol Biol Phys 2012;83:e87–92.
[22] Salama JK, Stenson KM, Kistner EO, et al. Induction chemotherapy and concurrent chemoradiotherapy for locoregionally advanced head and neck cancer: a multi-institutional phase II trial investigating three radiotherapy dose levels. Ann Oncol 2008;19:1787–94.

Please cite this article in press as: Nevens D et al. Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.08.009